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(56) Documents Cited
GB 2260134 A WO 95/23806 A2 WO 94/23718 A1 WO 91/10649 A1

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UK CL (Edition O) **C2C CKD CRB , C2P**
INT CL^6 **C07D , C07F**
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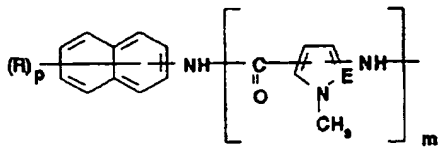
(54) **Antiviral ureido derivatives of substituted heterocyclic compounds**

(57) Ureido derivatives of substituted heterocyclic compounds having the following general formula (I)

B-CO-B (I)

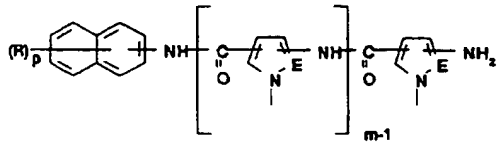
wherein each of the B groups, which are the same, is a group (i)



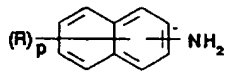
(i)

wherein
m is an integer of 1 to 6;
p is an integer of 1 to 3;
E is a group -CH= or -N=;
each of the R groups, which are the same, is a free or esterified acid group; and the pharmaceutically acceptable salts thereof;
and wherein when m is 1, then E is -N=; whereas when m is an integer of 2 to 6, then at least one of the E groups is -N=,
are useful eg. as anti-lentivirus agents.

Compounds of formulae:



(II)

and  (R is phosphonic) (III)

are novel intermediates.

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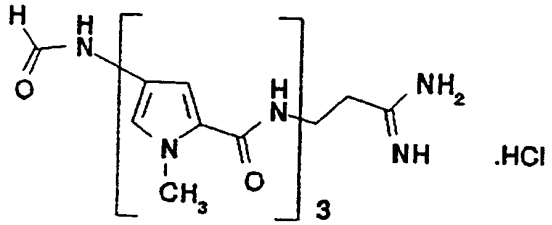
UREIDO DERIVATIVES OF SUBSTITUTED HETEROCYCLIC COMPOUNDS AND PROCESS FOR THEIR PREPARATION

The present invention relates to new ureido derivatives of substituted heterocyclic compounds, having biological activity, to a process for their preparation and to a pharmaceutical composition containing them.

The pyrrole derivatives of the invention may be regarded as derivatives of Distamycin A which is a known compound having the following formula

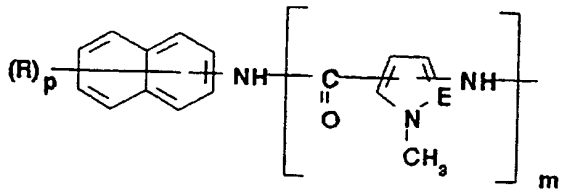


Literature referring to Distamycin A includes, for example NATURE 203, 1064 (1964).

The present invention provides ureido derivatives of substituted heterocyclic compounds having the following general formula (I)

B-CO-B (I)

wherein each of the B groups, which are the same, is a group (i)



(i)

wherein

m is an integer of 1 to 6;

p is an integer of 1 to 3;

E is a group -CH= or -N=;

each of the R groups, which are the same, is a free or esterified acid group; and the pharmaceutically acceptable salts thereof;

and wherein when m is 1, then E is -N=; whereas when m is an integer of 2 to 6, then at least one of the E groups is -N=.

The invention also includes within its scope all the possible isomers, stereoisomers and their mixtures and the metabolites and the metabolic precursors or bio-precursors of the compounds of formula (I).

The free, salified or esterified R groups may be on either or both the phenyl moieties of the naphthalene group.

Examples of R acidic groups, according to the present invention, for instance are those chosen from the group including sulfonic, phosphonic and carboxylic acid groups, the sulfonic and phosphonic acid groups being the preferred.

Esters of the acids of formula (I) are for instance alkyl and aryl-alkyl esters, having a branched or straight alkyl chain. C_1-C_6-alkyl and phenyl-C_1-C_6-alkyl esters, typically methyl, ethyl, propyl, iso-propyl, butyl, benzyl and phenylethyl esters are more preferred.

Examples of pharmaceutically acceptable salts are either those with inorganic bases, such as sodium, potassium, calcium and aluminum hydroxides, or with organic bases, such as lysine, arginine, N-methylglucamine, triethylamine, triethanolamine, dibenzylamine, methylbenzylamine, di-(2-ethylhexyl)amine, piperidine, N-ethylpiperidine, N,N-diethylaminoethylamine, N-ethylmorpholine, β-phenethylamine, N-benzyl-β-phenethylamine, N-benzyl-N,N-dimethylamine and the other acceptable organic amines. Sodium and potassium salts are preferred.

The substituted naphthyl groups are typically 1- or 2-aminonaphthyl groups.

When the naphthyl groups are substituted by three free,

esterified or salified acid groups, as defined above, the acid substituents are preferably in the 4,6,8-, 3,6,8-, 3,7,8- positions.

When they are substituted by two free, esterified or salified acid groups, the acid substituents are preferably in the 1,5-, 3,6-, 3,8-, 4,6-, 4,7-, 4,8-, 5,7- or 6,8- positions.

When they are substituted by one free, esterified or salified acid group, the acid substituent is preferably in the 1-, 2-, 3-, 4-, 5-, 6-, 7- or 8- position, of course is not linked to the amino position.

The substituted heterocyclic rings, containing substituent E, are typically amino - carbonyl disubstituted. The amino and carbonyl groups may be independently linked to any of the 2 to 5 carbon positions of the heterocyclic ring; of course, such groups are not both linked to the same carbon position. When E is -CH= , the disubstituted heterocycles are typically N-methyl-2,4-disubstituted pyrroles, preferably 1-methylpyrrole-4-amino-2-carbonyl and 1-methylpyrrole-2-amino-4-carbonyl derivatives. When E is -N=, the disubstituted heterocycles are typically N-methyl-3,5-disubstituted pyrazoles, preferably 1-methylpyrazole-3-amino-5-carbonyl and 1-methylpyrazole-5-amino-3-carbonyl derivatives.

As already said, the invention includes within its scope also the esters and the pharmaceutically acceptable salts of the acids of formula (I).

Only one or both of the two acidic functions of each phosphono $(HO)_2PO$-group are salified and/or esterified. In the salts of the invention preferably only one of the two acidic functions of each phosphono group is in a salified form, whereas in the esters of the invention both the two acidic functions of each phosphono group are preferably in an esterified form.

As stated above, the present invention also includes within its scope pharmaceutically acceptable bio-

precursors (otherwise known as pro-drugs) of the compounds of formula (I), i.e. compounds which have a different formula to formula (I) above but which nevertheless upon administration to a human being are converted directly or indirectly in vivo into a compound of formula (I).

Preferred compounds of the invention are the compounds of formula (I), wherein each of the B groups, which are the same, is a group (i) as defined above, wherein m is 2 or 3; one of the E groups is -N=, the others being -N= or -CH=; p is 2 or 3; and each of the R groups, which are the same, is a free or esterified phosphonic or sulfonic acid group; and the pharmaceutically acceptable salts thereof.

Examples of preferred compounds of the invention are:

Carbonylbis-2-({3-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-6,8-disulfonic acid;

Carbonylbis-2-({4-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-6,8-disulfonic acid;

Carbonylbis-2-({3-[(4-amino-1-methylpyrrole-2-carbonyl)amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-6,8-disulfonic acid;

Carbonylbis-2-({5-[(5-amino-1-methylpyrazole-3-carbonyl)amino]-1-methylpyrazole-3-carbonyl}amino)naphthalene-6,8-disulfonic acid;

Carbonylbis-2-({4-[(5-amino-1-methylpyrazole-3-carbonyl)amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-6,8-disulfonic acid;

Carbonylbis-2-({5-[(4-amino-1-methylpyrrole-2-carbonyl)amino]-1-methylpyrazole-3-carbonyl}amino)naphthalene-6,8-disulfonic acid;

Carbonylbis-1-({3-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-

4,6,8-trisulfonic acid;

Carbonylbis-1-({4-[(3-amino-1-methylpyrazole-5-carbonyl) amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-4,6,8-trisulfonic acid;

Carbonylbis-1-({3-[(4-amino-1-methylpyrrole-2-carbonyl) amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-4,6,8-trisulfonic acid;

Carbonylbis-1-({3-[(3-amino-1-methylpyrazole-5-carbonyl) amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-4,6-disulfonic acid;

Carbonylbis-1-({4-[(3-amino-1-methylpyrazole-5-carbonyl) amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-4,6-disulfonic acid;

Carbonylbis-1-({3-[(4-amino-1-methylpyrrole-2-carbonyl) amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-4,6-disulfonic acid;

Carbonylbis-2-({3-[(3-amino-1-methylpyrazole-5-carbonyl) amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-4,6,8-trisulfonic acid;

Carbonylbis-2-({4-[(3-amino-1-methylpyrazole-5-carbonyl) amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-4,6,8-trisulfonic acid;

Carbonylbis-2-({3-[(4-amino-1-methylpyrrole-2-carbonyl) amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-4,6,8-trisulfonic acid;

Carbonylbis-2-({3-[(3-amino-1-methylpyrazole-5-carbonyl) amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-1,5-disulfonic acid;

Carbonylbis-2-({4-[(3-amino-1-methylpyrazole-5-carbonyl) amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-1,5-disulfonic acid;

Carbonylbis-2-({3-[(4-amino-1-methylpyrrole-2-carbonyl) amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-1,5-disulfonic acid;

Carbonylbis-1-({3-[(3-amino-1-methylpyrazole-5-carbonyl) amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-8-sulfonic acid;

Carbonylbis-1-({4-[(3-amino-1-methylpyrazole-5-carbonyl) amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-8-sulfonic acid;

Carbonylbis-1-({3-[(4-amino-1-methylpyrrole-2-carbonyl) amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-8-sulfonic acid;

Carbonylbis-1-({3-[(3-amino-1-methylpyrazole-5-carbonyl) amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-4-sulfonic acid;

Carbonylbis-1-({4-[(3-amino-1-methylpyrazole-5-carbonyl) amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-4-sulfonic acid;

Carbonylbis-1-({3-[(4-amino-1-methylpyrrole-2-carbonyl) amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-4-sulfonic acid;

Carbonylbis-2-({3-[(3-amino-1-methylpyrazole-5-carbonyl) amino]-1-methylpyrazole-5-carbonyl}amino)-5-hydroxy naphthalene-7-sulfonic acid;

Carbonylbis-2-({4-[(3-amino-1-methylpyrazole-5-carbonyl) amino]-1-methylpyrrole-2-carbonyl}amino)-5-hydroxy naphthalene-7-sulfonic acid;

Carbonylbis-2-({3-[(4-amino-1-methylpyrrole-2-carbonyl) amino]-1-methylpyrazole-5-carbonyl}amino)-5-hydroxy naphthalene-7-sulfonic acid;

Carbonylbis-2-({4-[(3-amino-1-methylpyrazole-5-carbonyl) amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-4,6-disulfonic acid;

Carbonylbis-2-({4-[(3-amino-1-methylpyrazole-5-carbonyl) amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-5,7-disulfonic acid;

Carbonylbis-1-{[4-({4-[(3-amino-1-methylpyrazole-5-carbonyl)-amino]-1-methylpyrrole-2-carbonyl}amino)-1-methyl-pyrrole-2-carbonyl]amino}naphthalene-4,6-disulfonic acid;

Carbonylbis-2-{[4-({4-[(3-amino-1-methylpyrazole-5-carbonyl)-amino]-1-methylpyrrole-2-carbonyl}amino)-1-methyl-pyrrole-2-carbonyl]amino}naphthalene-4,6,8-

trisulfonic acid;

Carbonylbis-2-{[3-({4-[(4-amino-1-methylpyrrole-2-carbonyl)-amino]-1-methylpyrrole-2-carbonyl}amino)-1-methyl-pyrazole-5-carbonyl]amino}naphthalene-4,6,8-trisulfonic acid;

Carbonylbis-2-({3-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-4,8-diphosphonic acid;

Carbonylbis-2-({4-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-4,8-diphosphonic acid;

Carbonylbis-2-({3-[(4-amino-1-methylpyrrole-2-carbonyl)amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-4,8-diphosphonic acid;

Carbonylbis-1-({3-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-4,6-diphosphonic acid;

Carbonylbis-1-({4-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-4,6-diphosphonic acid;

Carbonylbis-1-({3-[(4-amino-1-methylpyrrole-2-carbonyl)amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-4,6-diphosphonic acid;

Carbonylbis-1-({3-[(4-amino-1-methylpyrrole-2-carbonyl)amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-6,8-diphosphonic acid;

Carbonylbis-1-({3-[(4-amino-1-methylpyrrole-2-carbonyl)amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-5,7-diphosphonic acid;

Carbonylbis-2-{[4-({4-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrrole-2-carbonyl}amino)-1-methylpyrrole-2-carbonyl]amino}naphthalene-4,8-diphosphonic acid;

Carbonylbis-1-{[4-({4-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrrole-2-carbonyl}amino)-1-methylpyrrole-2-carbonyl]amino}naphthalene-4,6-diphosphonic acid;

Carbonylbis-2-{[4-({4-[(5-amino-1-methylpyrazole-3-carbonyl)amino]-1-methylpyrrole-2-carbonyl}amino)-1-methylpyrrole-2-carbonyl]amino}naphthalene-4,8-diphosphonic acid;

Carbonylbis-1-({4-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-6,8-diphosphonic acid;

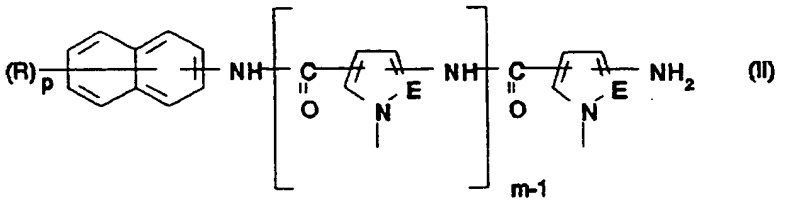
Carbonylbis-1-({4-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-5,7-diphosphonic acid;

and the C_1-C_6-alkyl and phenyl-C_1-C_6-alkyl esters and the pharmaceutically acceptable salts thereof.

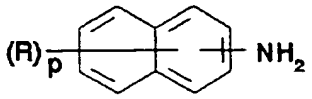
Particularly preferred are the methyl, ethyl and benzyl esters and the sodium and potassium salts of the said examples of specific compounds of the invention.

The compounds of formula (I) and the pharmaceutically acceptable salts thereof are hereafter also referred to as "the compounds of the invention" or as "the active agents of the invention".

The compounds of the invention, and the salts thereof can be prepared by a process comprising reacting a compound of formula (II) or (III), respectively



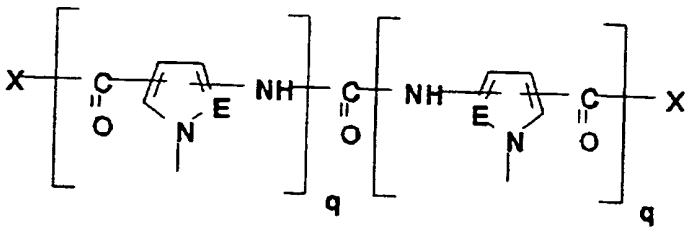
(II)



(III)

wherein

m, p, E and R are as defined above, or a salt thereof, with a compound of formula (IV)



(IV)

wherein

each of the X groups, which may be the same or different, is a good leaving group, E is as defined above, q is 0 to 6 and wherein, when a compound of formula (IV) is reacted with a compound of formula (II), then q is 0 to 5 in such a way that [q+(m-1)] is 0 to 5, whereas when a compound of formula (IV) is reacted with a compound of formula (III), then q is an integer of 1 to 6 and, if desired, converting a compound of formula (I) into another compound of formula (I), and/or, if desired, salifying a compound of formula (I) thus obtained, and/or, if desired, obtaining a free acid of formula (I) from an ester or a salt thereof, and/or, if desired, esterifying an acid of formula (I).

A salt of a compound of formula (II) or (III) may be a salt with organic or inorganic bases, for example those mentioned above as to the pharmaceutically acceptable salts of the invention, the sodium and potassium salts being the preferred.

Compounds of formula (IV) are known products or may be easily obtained according to known methods from known products.

Preferred examples of good leaving groups, according to the meaning of X, are halogen atoms, in particular chlorine, or other easily displaceable groups such as, imidazolyl, triazolyl, p-nitrophenoxy or trichlorophenoxy.

The reaction of a compound of formula (II) or (III), or a salt thereof, with a compound of formula (IV) is an analogy process and can be carried out according to well known methods; for example according to the conditions

described in organic chemistry for this kind of reaction, i.e. for synthesis of urea derivatives. Preferably the reaction may be carried out at a molar ratio of compound (II) or (III), or a salt thereof : compound (IV) from about 1 : 0.5 to about 1 : 4. According to a preferred embodiment of the invention, when the compound of formula (IV) is phosgene, bis(trichloromethyl)carbonate or trichloromethyl chloroformate can be used as a phosgene source, according to known methods.

The reaction is preferably performed in an organic solvent, such as dichloromethane, dichloroethane, chloroform, toluene, or dimethylsulphoxyde, dimethylformamide, dimethylacetamide, hexamethylphosphoramide, or their aqueous mixtures, or in water/dioxane, water/toluene or water/dichloromethane mixtures, in the presence of either an organic base such as triethylamine, diisopropylethylamine or pyridine or an inorganic base such as sodium bicarbonate or sodium acetate or a convenient buffer as known in the art. The reaction temperature may vary from about -10°C to about 150°C and the reaction time from about 1 to 24 hours.

The compounds of formula (I) prepared according to the above described procedures may be purified by conventional methods such as by silica gel, alumina or reversed phase column chromatography, and/or by recrystallization from organic solvents such as lower aliphatic alcohols or dimethylformamide or their mixtures or in water containing mixtures.

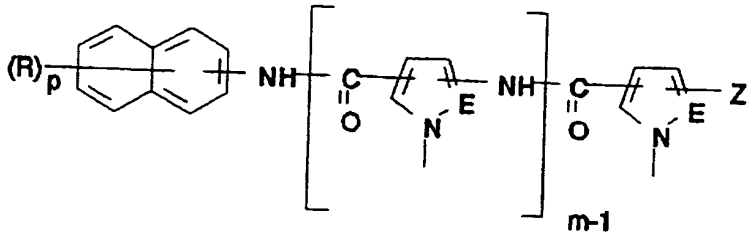
Analogously, esterification or salification of an acid of formula (I) can be carried out by known methods in the art.

The compounds of formula (II), and the salts thereof, are new compounds and are a further object of the present invention.

The compounds of formula (II), and the salt thereof, can be obtained according to analogy processes.

For instance, a compound of formula (II) can be obtained

by deprotection or reduction of a compound of formula (V) or a salt thereof



(V)

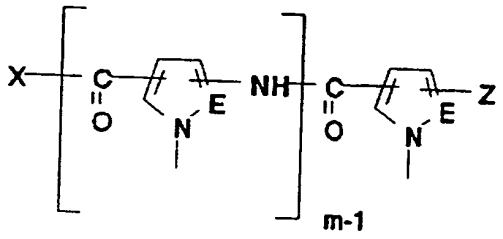
wherein

Z is a protected amino group according to the chemistry of peptides, or a group generating an amine function by reduction, such as $-NHCOOCH_2Ph$ or NO_2,

m, p, E and R are as defined above;

by methods well known in the art.

The compounds of formula (V) can be obtained by reacting an amine of formula (III) as defined above, or a salt thereof as defined above, with a compound of formula (VI)



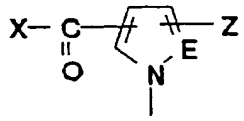
(VI)

wherein

m, E, Z and X are as defined above.

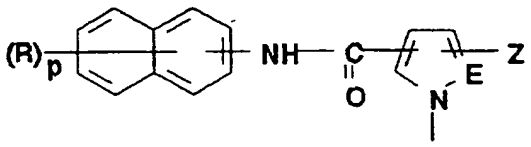
Also the reaction of an amine of formula (III), or a salt thereof, with a compound of formula (VI) is a well known process.

Alternatively, a compound of formula (V) wherein m is 2, 3, 4, 5 or 6 may be obtained by a multi-step-process comprising reacting a compound of formula (VII)



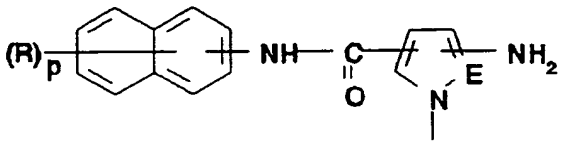
(VII)

wherein
E, Z and X are as defined above,
with an amine of formula (III),or a salt thereof, as defined above. The reaction, which may be carried out according to known methods, provides a compound of formula (VIII) or a salt thereof



(VIII)

wherein
Z, E, R and p are as defined above.
A compound of formula (VIII), or a salt thereof, can be deprotected or reduced according to known methods to provide a compound of formula (IX), or a salt thereof



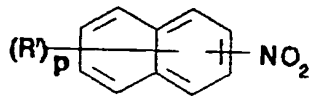
(IX)

wherein E, p and R are as defined above,
which in its turn is reacted with a compound of formula (VII), as defined above, thus obtaining a compound of formula (V), as defined above, wherein m is 2. If a compound of formula (V), wherein m is 3, 4, 5 or 6 is desired, further deprotection or reduction and acylation steps are required.
The compounds of formula (VI) are known compounds or may be obtained, for example, according to Heterocycles, vol. 27, No. 8, p. 1945-52 (1988).

The compounds of formula (VII) are known products or may be easily obtained according to known methods.

The amines of formula (III) as defined above and the salts thereof, wherein R is a carboxylic or a sulfonic acid groups are known compounds, for instance the sulfonic ones are described in PCT/EP91/00014. Those wherein R is a phosphonic acid group are new compounds and are a further object of this invention.

An amine of formula (III) wherein R is a free, salified or esterified phosphonic acid group, now indicated as R', and p is as defined above, or a salt thereof, can be obtained by reducing a nitro derivative of formula (X) or a salt thereof



(X)

wherein R' and p are as defined above,

according to known methods.

A nitro derivative of formula (X) can be obtained by nitration of a suitable free, esterified or salified mono-, di- or tri-phosphonic naphthalenic acid. In its turn said free, esterified or salified acid can be obtained by reacting a naphthalene compound substituted by 1, 2 or 3 trifluoromethanesulfonate group(s) or halogen atom(s), e.g. bromine or iodine, respectively with a di-C_1-C_6-alkyl-, di-aryl-, e.g. di-phenyl- or di-aryl-alkyl, e.g. di-phenyl -C_1-C_6-alkyl phosphite, in the presence of an organic basic agent, e.g. triethylamine, diisopropylamine or pyridine, and a suitable catalytic agent, e.g. tetrakis(triphenylphosphine) palladium(0), platinum(0) or nickel(0), at a temperature ranging from about 0°C to about 150°C.

A naphthalene compound substituted by 1, 2 or 3 trifluoromethanesulfonate groups can be obtained by reacting a mono-, di- or tri-hydroxy substituted naphthalene

compound, respectively, with a reactive trifluoromethanesulfolic acid derivative, e.g. the chloride or anhydride, in the presence of an organic basic agent, e.g. pyridine or triethylamine, if the case in an organic inert solvent, e.g. dichloromethane, diethylether or toluene. Alternatively a compound substituted by one, two or three trifluoromethanesulfonate or halogen group(s) can be nitrated with known methods and the nitro derivative thus obtained subjected to reaction with di-alkyl(aryl) phosphite as above reported, to obtain the formula (X) derivative.

A salt of a compound of formula (II), (III), (V), (VIII), (IX) or (X) may be a salt with organic or inorganic bases, for example those mentioned above as to the compounds of formula (I), the sodium and potassium salts being the preferred ones.

PHARMACOLOGY

The new compounds of formula (I), and the pharmaceutically acceptable salts thereof, according to the present invention, are angiogenesis inhibitors, as shown, e.g., by the fact that they have been found to be active in the chorioallantoic membrane test, according to the Folkman's method [Nature, 297, 307 (1982)]. Therefore the compounds of the present invention are useful in treating several pathological conditions in mammals, including humans, where the growth of new blood vessels is detrimental, for example, in chronic inflammation, diabetic retinopathy, psoriasis, rheumatoid arthritis and tumor growth. In particular, in the cancer therapy the compounds of the invention can be administered alone or in association with antitumor agents such as doxorubicin, etoposide, fluorouracil, melphalan, 4'-iododoxorubicin, methoxy-morpholino-doxorubicin, cyclophosphamide, bleomycin, vinblastin or mitomycin.

The compounds of the present invention have also been

found to be endowed with TNFα-neutralizing activity and therefore they can be employed in humans for prophylactic and/or therapeutic use in any disease state in which TNFα is known to play a detrimental role. Typically such disease states are cachexia, septic shock, graft-versus-host disease, multiple sclerosis, anti-CD3 monoclonal antibody-induced cytokine-release syndrome, AIDS, cerebral malaria, rheumatoid arthritis. The TNFα-inhibiting activity of the compounds according to the present invention is proven, for instance, by the fact that they are active in inhibiting the cytotoxicity activity of human TNFα on untreated mouse LM cells.

Accordingly, the new compounds of the invention can be used as angiogenesis inhibitors and/or as TNFα-neutralizing activity agents. The compounds of the invention can thus be used in the preparation of a medicament for use in the treatment of angiogenesis and/or for prophylactic and/or therapeutic use in a disease state in which TNFα plays a detrimental role. In these therapeutical applications the compounds of the invention can be administered by the usual routes, for example, parenterally, e.g. by intravenous injection or infusion, intramuscularly, subcutaneously, topically or orally. The dosage depends on the age, weight and conditions of the patient and on the administration route. For example, a suitable dosage for administration to adult humans may range from about 0.5 to about 300 mg pro dose 1-4 times a day.

Moreover, the compounds of the present invention have been found to act directly as anti-lentivirus agents, in particular against Human Immunodeficiency Virus (HIV). For instance, the representative compounds of the invention Carbonylbis-2-({4-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrrole-2-carbonyl}amino) naphthalene-6,8 disulfonic acid, Carbonylbis-2-({3-[(3-amino-1-methyl-pyrazole-5-carbonyl)amino]-1-methyl pyrazole-5-carbonyl}amino)naphthalene-6,8-disulfonic

acid, Carbonylbis-2-({3-[(4-amino-1-methylpyrrole-2-carbonyl)amino]-1-methylpyrazole-5-carbonyl}amino) naphthalene-6,8-disulfonic acid and Carbonylbis-2-{[4-({4-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrrole-2-carbonyl}amino)-1-methylpyrrole-2-carbonyl]amino}naphthalene-4,8-diphosphonic acid have been found to be active in the biological test described in J. Natl. Cancer Inst. 81, 557-586 (1989). A human patient suffering from lentivirus infection can thus be treated by a method comprising administering thereto an effective amount of a compound of the invention. In this way, the compounds of the invention can be used to treat an infection attributable to a lentivirus, in particular a human immunodeficiency virus, especially HIV-1 or HIV-2.

The compounds of the invention can also be used in the preparation of a medicament for use in the treatment of a human patient suffering from lentivirus infection. The said medicament may be for use as an anti-lentivirus agent, for example an anti-HIV-1 or -HIV-2 agent. The said medicament may also be for use in ameliorating the symptoms of lentivirus-induced disease in a human patient suffering from lentivirus infection.

In particular the compounds of the invention can be used in the preparation of an agent to be used in the treatment of a human patient who is seropositive diseased, stressed or pathological as a result of infection with a lentivirus, in particular HIV, or who is suffering from induced disease, e.g., lymphoadenopathy syndrome (LS), AIDS-related complex (ARC), AIDS or Kaposi's sarcoma. The condition of a human patient can thus be ameliorated or improved.

In these therapeutical applications the compounds of the invention can be administered by usual routes, for example, parenterally, e.g. by intravenous injection or infusion, intramuscularly, subcutaneously, topically or orally, intravenous injection or infusion being

preferred. The dosage depends on the age, weight and condition of the patient and on the administration route. A suitable dosage for the compounds of the invention, for example Carbonylbis-2-({3-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrazole-5-carbonyl}amino) naphthalene-6,8-disulfonic acid or a pharmaceutically acceptable salt thereof, for administration to adult humans is from about 0.4 to about 280 mg per dose 1-4 times a day.

The compounds of the invention may be used in a method of treatment of the above mentioned pathological conditions comprising both separate and substantially contemporaneous administration of a composition containing a compound of formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutical composition containing different pharmaceutically active agents. The present invention therefore further provides products comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, and a second active agent as a combined preparation for separate, simultaneous or sequential use in treating a human patient suffering from lentivirus infection, in particular infection with HIV. The second active agent is typically a drug that affects the pathogenesis of HIV-induced diseases.

For example, the compounds of the invention may be employed with various active agents, in particular those that affect reverse transcriptase, antimicrobial and antitumor agents or a mixture of two or more thereof. Drugs of interest include non-nucleoside reverse transcriptase inhibitors, e.g. nevirapine; nucleoside derivatives, e.g. zidovudine and didanosine; acyclovir; ribavirin; ascorbic acid; protease inhibitors; cytokine, e.g. IL-1, IL-2, IL-3 or IL-4; growth factors; interferons, e.g. alpha- or gamma-interferon; antitumor agents, e.g. doxorubicin, daunomycin, epirubicin, 4'-iododoxorubicin, methoxy-morpholino-doxorubicin, idarubicin, etoposide, fluorouracil, melphalan, cyclo-

phosphamide, bleomycin, vinblastin and mitomycin; immunomodulating agents, in particular immunostimulants, gamma globulin, immune globulin and monoclonal antibody products, antibiotics and antimicrobial products.

Typically, the antimicrobial agents may include a penicillin in conjunction with an aminoglycoside (e.g. gentamycin, tobramycin).

However several well known additional agents, e.g. cephalosporin, can be utilized.

The administration dosage of these drugs will vary, depending upon the disease status of the individual. The dosage regimen must therefore be tailored to the particular of the patient's conditions, response and associate treatments in a manner which is conventional for any therapy, and may need to be adjusted in response to changes in conditions and/or in light of other clinical conditions.

The pharmaceutical composition used in the invention may comprise a compound of formula (I) or pharmaceutically acceptable salt thereof, as the active substance, in association with one or more pharmaceutically acceptable excipients and/or carriers. The pharmaceutical compositions are usually prepared following conventional methods and are administered in a pharmaceutically suitable form. For instance, solutions for intravenous injection or infusion may contain as carrier, for example, sterile water or, preferably, they may be in the form of sterile aqueous isotonic saline solutions. Suspensions or solutions for intramuscular injections may contain, together with the active compound, a pharmaceutically acceptable carrier, e.g. sterile water, olive oil, ethyl oleate, glycols, e.g. propylene glycol, and, if desired, a suitable amount of lidocaine hydrochloride.

In the form for topical application, e.g. creams, lotions or pastes for use in dermatological treatment, the active ingredient may be mixed with conventional oleaginous or

emulsifying excipients.

The solid oral forms, e.g. tablets and capsules, may contain, together with the active compound, diluents, e.g. lactose, dextrose, saccharose, cellulose, corn starch and potato starch; lubricants, e.g. silica, talc, stearic acid, magnesium or calcium stearate, and/or polyethylene glycols; binding agents, e.g. starches, arabic gum, gelatin, methylcellulose, carboxymethyl-cellulose, polyvinylpyrrolidone; disaggregating agents, e.g. a starch, alginic acid, alginates, sodium starch glycolate; effervescing mixtures; dyestuffs; sweeteners; wetting agents, for instance, lecithin, polysorbates, laurylsulphates; and, in general, non-toxic and pharmacologically inactive substances used in pharmaceutical formulations. Said pharmaceutical preparations may be manufactured in a known manner, for example by means of mixing, granulating, tabletting, sugar-coating, or film-coating processes.

The following examples illustrate but do not limit the invention.

Example 1

2-{[3-(Benzyloxycarbonyl)amino-1-methylpyrazole-5-carbonyl]amino}naphthalene-6,8-disulfonic acid dipotassium salt [Compound (VIII), R= $-SO_3H$, p= 2, Z= $-NHCOOCH_2Ph$, E= -N=].

To a solution of 2-aminonaphthalene-6,8-disulfonic acid mono-potassium salt (85% technical, 1.03 g, 2.55 mmol), potassium bicarbonate (1.00 g, 10 mmol) in water (25 ml) and 1,4-dioxane (10 ml) a solution of 3-(benzyloxy-carbonyl)amino-1-methylpyrazole-5-carboxylic acid chloride (obtained by treating the acid with $SOCl_2$) (0.88 g, 3.0 mmol) in 1,4-dioxane (10 ml) is added dropwise, with stirring, at room temperature. The reaction mixture is diluted with water, dioxane is evaporated under

reduced pressure and to the resulting aqueous solution (25 ml) potassium acetate (3 g) is added thus obtaining a microcrystalline precipitate which, after ice-cooling, is filtered, washed with ice-cooled 30% potassium acetate solution, then with ethanol and vacuum dried over phosphorus pentoxide to give the title compound (1.46 g, 90% yield).

^{1}H NMR (DMSO-d_6): δ 10.6 (br s, 1H, exchangeable with D_2O); 10.1 (br s, 1H, exch. with D_2O); 9.01 (d, 1H); 8.27 (d, 1H); 8.06 (m, 1H); 7.89 (m, 2H); 7.4 (m, 5H); 7.26 (s, 1H); 5.18 (s, 2H); 4.01 (s, 3H).

Example 2

2-[(3-Amino-1-methylpyrazole-5-carbonyl)amino] naphthalene-6,8-disulfonic acid monopotassium salt [Compound (IX), R= $-SO_3H$, p= 2, E= -N=].

A solution of 2-{[3-(benzyloxycarbonyl)amino-1-methyl pyrazole-5-carbonyl]amino}naphthalene-6,8-disulfonic acid dipotassium salt of Example 1 (1.44 g, 2.26 mmol) in H_2O (350 ml) and hydrochloric acid (2.25 ml 1 N) is hydrogenated in a PARR apparatus over 45 psi hydrogen pressure at room temperature in the presence of 5% Pd/C catalyst (500 mg). After catalyst filtration, the solution is concentrated in vacuum to 40 ml and, after ice-cooling, the precipitated solid is filtered, washed with ice-cooled water and dried in vacuum over P_2O_5 thus obtaining the title compound as a white microcrystalline solid (805 mg, 76.5% yield).

^{1}H NMR (DMSO-d_6): δ 10.7(s, 1H, exch. with D_2O); 8.94 (d, 1H, J=0.5 Hz); 8.28 (d, 1H, J=1.7 Hz); 8.06 (d, 1H, J=1.4 Hz); 7.93 (m, 2H); 7.04 (s, 1H); 4.06 (s, 3H).

Example 3

2-({3-[(3-Amino-1-methylpyrazole-5-carbonyl)amino]-1-methyl pyrazole-5-carbonyl}amino)naphthalene-6,8-disulfonic acid monopotassium salt [Compound (II), R=

—SO_3H, p= 2, m= 2, E= -N=].

To a solution of 2-[(3-amino-1-methylpyrazole-5-carbonyl)amino]naphthalene-6,8-disulfonic acid monopotassium salt of Example 2 (1.02 g, 2.2 mmol) and potassium bicarbonate (1.00 g, 10 mmol) in water (40 ml) and 1,4-dioxane (15 ml), a solution of 3-(benzyloxy carbonyl)amino-1-methylpyrazole-5-carboxylic acid chloride (735 mg, 2.5 mmol) in 1,4-dioxane (10 ml) is added dropwise, with stirring, at room temperature. The reaction mixture is diluted with water, 1,4-dioxane is evaporated under reduced pressure and concentrated to a final volume of 30 ml. After ice-cooling, the resulting microcrystalline precipitate is filtered, washed with ice-cooled water and dissolved in water (500 ml). The resulting solution, after hydrochloric acid addition (2.5 ml 1N), is hydrogenated in a PARR apparatus with 5% Pd/C catalyst (350 mg) at room temperature and 45 psi hydrogen pressure. After catalyst filtration, the solution is concentrated under reduced pressure to 25 ml and ice-cooled. The precipitated white solid is filtered, washed with ice-cooled water, with ethanol and dried in vacuum over P_2O_5 thus obtaining the title compound as a white microcrystalline solid (665 mg, 51.5% yield).

^1H NMR (DMSO-d_6, 50°C): δ 11.03 (s, 1H, exch. with D_2O); 10.63 (s, 1H, exch. with D_2O); 8.99 (s, 1H); 8.26 (d, 1H, J=1.7 Hz); 8.04 (m, 1H); 7.90 (m, 2H); 7.58 (s, 1H); 6.94 (s, 1H); 4.08 (s, 3H); 4.05 (s, 3H).

Example 4

Carbonylbis-2-({3-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-6,8-disulfonic acid tetrapotassium salt [Compound (I), R= -SO_3H, p= 2, m= 2, E= -N=].

To a solution of 2-({3-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrazole-5-carbonyl}amino)

naphthalene-6,8-disulfonic acid monopotassium salt of Example 3 (500 mg, 0.85 mmol), potassium bicarbonate (850 mg, 8.5 mmol) in water (50 ml) and 1,4-dioxane (10 ml) a solution of bis(trichloromethyl)carbonate (250 mg, 0.85 mmol) in 1,4-dioxane (10 ml) is added dropwise, with stirring, at room temperature over 2 hrs. The reaction mixture is diluted with water, the dioxane is evaporated under reduced pressure and concentrated to a final volume of 25 ml. After ice-cooling the resulting precipitate is filtered, washed with ice-cooled water and vacuum dried over P_2O_5 thus obtaining the title compound (470 mg, 86% yield).

^{1}H NMR (DMSO-d_6): δ 11.2 (bs, 1H, exch. with D_2O); 10.7 (bs, 1H, exch. with D_2O); 9.3 (bs, 1H, exch. with D_2O); 8.98 (s, 1H); 8.21 (d, 1H, J=1.7 Hz); 8.03 (nm, 1H); 7.90 (m, 2H); 7.60 (s, 1H); 7.04 (s, 1H); 4.08 (s, 3H); 4.03 (s, 3H).

By proceeding analogously, with the appropriate starting materials, the following sodium or potassium salts of the compounds can be obtained:

Carbonylbis-2-({5-[(5-amino-1-methylpyrazole-3-carbonyl)amino]-1-methylpyrazole-3-carbonyl}amino) naphthalene-6,8-disulfonic acid;

Carbonylbis-2-({4-[(5-amino-1-methylpyrazole-3-carbonyl)amino]-1-methylpyrrole-2-carbonyl}amino) naphthalene-6,8-disulfonic acid;

Carbonylbis-2-({5-[(4-amino-1-methylpyrrole-2-carbonyl)amino]-1-methylpyrazole-3-carbonyl}amino) naphthalene-6,8-disulfonic acid;

Carbonylbis-1-({3-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrazole-5-carbonyl}amino) naphthalene-4,6,8-trisulfonic acid;

Carbonylbis-1-({3-[(4-amino-1-methylpyrrole-2-carbonyl)amino]-1-methylpyrazole-5-carbonyl}amino) naphthalene-4,6,8-trisulfonic acid;

Carbonylbis-1-({4-[(3-amino-1-methylpyrazole-5-carbonyl) amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-4,6,8-trisulfonic acid;

Carbonylbis-1-({3-[(3-amino-1-methylpyrazole-5-carbonyl) amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-4,6-disulfonic acid;

Carbonylbis-1-({4-[(3-amino-1-methylpyrazole-5-carbonyl) amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-4,6-disulfonic acid;

Carbonylbis-1-({3-[(4-amino-1-methylpyrrole-2-carbonyl) amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-4,6-disulfonic acid;

Carbonylbis-2-({3-[(3-amino-1-methylpyrazole-5-carbonyl) amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-4,6,8-trisulfonic acid;

Carbonylbis-2-({4-[(3-amino-1-methylpyrazole-5-carbonyl) amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-4,6,8-trisulfonic acid;

Carbonylbis-2-({3-[(4-amino-1-methylpyrrole-2-carbonyl) amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-4,6,8-trisulfonic acid;

Carbonylbis-2-({3-[(3-amino-1-methylpyrazole-5-carbonyl) amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-1,5-disulfonic acid;

Carbonylbis-2-({4-[(3-amino-1-methylpyrazole-5-carbonyl) amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-1,5-disulfonic acid;

Carbonylbis-2-({3-[(4-amino-1-methylpyrrole-2-carbonyl) amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-1,5-disulfonic acid;

Carbonylbis-1-({3-[(3-amino-1-methylpyrazole-5-carbonyl) amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-8-sulfonic acid;

Carbonylbis-1-({4-[(3-amino-1-methylpyrazole-5-carbonyl) amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-8-sulfonic acid;

Carbonylbis-1-({3-[(4-amino-1-methylpyrrole-2-carbonyl)

amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-8-sulfonic acid;

Carbonylbis-1-({3-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-4-sulfonic acid;

Carbonylbis-1-({4-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-4-sulfonic acid;

Carbonylbis-1-({3-[(4-amino-1-methylpyrrole-2-carbonyl)amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-4-sulfonic acid;

Carbonylbis-2-({3-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrazole-5-carbonyl}amino)-5-hydroxy-naphthalene-7-sulfonic acid;

Carbonylbis-2-({4-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrrole-2-carbonyl}amino)-5-hydroxy-naphthalene-7-sulfonic acid;

Carbonylbis-2-({3-[(4-amino-1-methylpyrrole-2 carbonyl)amino]-1-methylpyrazole-5-carbonyl}amino)-5-hydroxy-naphthalene-7-sulfonic acid;

Carbonylbis-2-({4-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-4,6-disulfonic acid;

Carbonylbis-2-({4-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-5,7-disulfonic acid;

Carbonylbis-1-{[4-({4-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrrole-2-carbonyl}amino)-1-methylpyrrole-2-carbonyl]amino}naphthalene-4,6-disulfonic acid;

Carbonylbis-2-{[4-({4-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrrole-2-carbonyl}amino)-1-methylpyrrole-2-carbonyl]amino}naphthalene-4,6,8-trisulfonic acid; and

Carbonylbis-2-{[3-({4-[(4-amino-1-methylpyrrole-2-carbonyl)amino]-1-methylpyrrole-2-carbonyl}amino)-1-methylpyrazole-5-carbonyl]amino}naphthalene-4,6,8-

trisulfonic acid.

Example 5

2-[(4-amino-1-methylpyrrole-2-carbonyl)amino]naphthalene-6, 8-disulfonic acid monopotassium salt [Compound (IX), R= $-SO_3H$, p= 2, E= -CH=].

To a solution of 2-aminonaphthalene-6,8-disulfonic acid mono-potassium salt (technical 85%, 3.41 g, 8.5 mmol), potassium bicarbonate (2.70 g, 27 mmol) in water (80 ml) and 1,4-dioxane (40 ml) a solution of 4-nitro-1-methyl-pyrrole-2-carboxylic acid chloride (1.90 g, 10 mmol) (obtained by treating the acid with thionyl chloride) in 1,4-dioxane (40 ml) is added dropwise, with stirring, at room temperature. The precipitated solid is filtered, washed and dried to give the 4-nitro-derivative as dipotassium salt (4.50 g) in near quantitative yield [Compound (VIII), R= $-SO_3H$, p= 2, Z= $-NO_2$, E= -CH=].

^1H NMR (DMSO-d_6): δ 10.50 (bs, 1H, exch. with D_2O); 8.98 (s, 1H); 8.27 (d, 1H, J=1.7 Hz); 8.19 (d, 1H, J=1.7 Hz); 7.90 (m, 2H); 7.82 (d, 1H, J=1.9 Hz); 3.99 (s, 3H).

The above compound (2.13 g, 4 mmol) dissolved in H_2O (300 ml) and hydrochloric acid (5.0 ml 1N) is hydrogenated in a PARR apparatus over 45 psi hydrogen pressure at room temperature in the presence of 5% Pd/C catalyst (500 mg). After catalyst filtration, the solution is concentrated in vacuum to 30 ml and, after ice-cooling, the precipitated solid is filtered, washed with ice-cooled water and dried over P_2O_5 to obtain the title compound as a white microcrystalline solid (1.02 g, 55% yield).

^1H NMR (DMSO-d_6): δ 10.25 (s, 1H, exch. with D_2O) 9.75 (br, 3H, exch. with D_2O); 8.91 (s, 1H); 8.28 (d, 1H); 8.05 (d, 1H); 7.90 (nm, 2H); 7.15 (m, 2H); 3.92 (s, 3H).

Example 6

3,3'-Carbonylbis-[5-(N-imidazolecarbonyl)-3-amino-1-methyl pyrazole] [Compound (IV), q= 1, X= imidazolyl, E= -N=].

To a solution of 3-amino-1-methylpyrazole-5-carboxylic acid (220 mg, 1.56 mmol), sodium bicarbonate (420 mg, 5 mmol) in water (10 ml) and 1,4-dioxane (3 ml) a solution of bis(trichloromethyl)carbonate (86 mg, 0.29 mmol) in 1,4-dioxane (2 ml) is added dropwise, with stirring and ice-cooling. The reaction mixture is brought to pH 1-2 with diluted hydrochloric acid, the precipitated solid is filtered, washed with water and dried to give 3,3'-carbonylbis-3-amino-1-methylpyrazole-5-carboxylic acid (180 mg, 75% yield).

^{1}H NMR (DMSO-d_6): δ 14-12.5 (br, 1H, exch. with D_2O); 9.16 (bs, 1H, exch. with D_2O); 6.81 (s, 1H); 3.96 (s, 3H).

To a solution of the above acid (150 mg, 0.52 mmol) in DMF (3 ml) N,N'-carbonyldiimidazole (195 mg, 1.2 mmol) is added portionwise, with stirring, at room temperature. After 3 hrs, anhydrous Et_2O is added and the precipitated solid is filtered, washed and dried to give the title compound (170 mg, 80% yield).

^{1}H NMR (DMSO-d_6): δ 9.35 (s, 1H, exch. with D_2O); 8.30 (m, 1H); 7.73 (t, 1H); 7.17 (q, 1H); 6.92 (s, 1H); 3.98 (s, 3H).

Example 7

Carbonylbis-2-({4-[(3-amino-1-methylpyrazole-5-carbonyl) amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-6,8-disulfonic acid tetrasodium salt [Compound (I), R= $-SO_3H$, p= 2, m= 2, E= -N= and -CH=].

A mixture of 2-[(4-amino-1-methylpyrrole-2-carbonyl) amino]naphthalene-6,8-disulfonic acid monopotassium salt

of Example 5 (278 mg, 0.6 mmol) and 3,3'-carbonylbis-[5-(N-imidazolecarbonyl)-3-amino-1-methylpyrazole] of Example 6 (118 mg, 0.29 mmol) in DMF (10 ml) is warmed under N_2 at 55-65°C for 3 hrs. Dimethylformamide is distilled in vacuum, ethanol added to the residue and the precipitated solid filtered and washed. The crude is dissolved in water, passed through a sulfonic acid ion-exchange resin in H^+ form, the acid eluate of the title compound is neutralized to pH 7.0 with NaOH solution and purified with reversed-phase liquid chromatography eluting with a gradient from H_2O to H_2O:methanol 80:20. The product containing eluate is concentrated in vacuum and freeze-dried to give the yellow amorphous title compound (240 mg, 66% yield).

^1H NMR (DMSO-d_6): δ 10.52 (s, 1H, exch. with D_2O); 10.26 (s, 1H, exch. with D_2O); 9.43 (bs, 1H, exch. with D_2O); 8.91 (s, 1H); 8.21 (d, 1H, J=1.7 Hz); 8.00 (nm, 1H,); 7.86 (m, 2H); 7.34 (d, 1H, J=1.7 Hz); 7.28 (d, 1H, J=1.7 Hz); 7.06 (s, 1H); 4.02 (s, 3H); 3.89 (s, 3H).

By proceeding analogously ,with the appropriate starting materials, the following compounds can be obtained either as a free or sodium salified acids:

Carbonylbis-2-({5-[(5-amino-1-methylpyrazole-3-carbonyl) amino]-1-methylpyrazole-3-carbonyl}amino)naphthalene-6,8-disulfonic acid;

Carbonylbis-2-({4-[(5-amino-1-methylpyrazole-3-carbonyl) amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-6,8-disulfonic acid;

Carbonylbis-2-({5-[(4-amino-1-methylpyrrole-2-carbonyl) amino]-1-methylpyrazole-3-carbonyl}amino)naphthalene-6,8-disulfonic acid;

Carbonylbis-1-({3-[(3-amino-1-methylpyrazole-5-carbonyl) amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-4,6,8-trisulfonic acid;

Carbonylbis-1-({3-[(4-amino-1-methylpyrrole-2-carbonyl)

amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-4,6,8-trisulfonic acid;

Carbonylbis-1-({4-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-4,6,8-trisulfonic acid;

Carbonylbis-1-({3-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-4,6-disulfonic acid;

Carbonylbis-1-({4-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-4,6-disulfonic acid;

Carbonylbis-1-({3-[(4-amino-1-methylpyrrole-2-carbonyl)amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-4,6-disulfonic acid;

Carbonylbis-2-({3-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-4,6,8-trisulfonic acid;

Carbonylbis-2-({4-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-4,6,8-trisulfonic acid;

Carbonylbis-2-({3-[(4-amino-1-methylpyrrole-2-carbonyl)amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-4,6,8-trisulfonic acid;

Carbonylbis-2-({3-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-1,5-disulfonic acid;

Carbonylbis-2-({4-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-1,5-disulfonic acid;

Carbonylbis-2-({3-[(4-amino-1-methylpyrrole-2-carbonyl)amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-1,5-disulfonic acid;

Carbonylbis-1-({3-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-8-sulfonic acid;

Carbonylbis-1-({4-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-8-

sulfonic acid;

Carbonylbis-1-({3-[(4-amino-1-methylpyrrole-2-carbonyl) amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-8-sulfonic acid;

Carbonylbis-1-({3-[(3-amino-1-methylpyrazole-5-carbonyl) amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-4-sulfonic acid;

Carbonylbis-1-({4-[(3-amino-1-methylpyrazole-5-carbonyl) amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-4-sulfonic acid;

Carbonylbis-1-({3-[(4-amino-1-methylpyrrole-2-carbonyl) amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-4-sulfonic acid;

Carbonylbis-2-({3-[(3-amino-1-methylpyrazole-5-carbonyl) amino]-1-methylpyrazole-5-carbonyl}amino)-5-hydroxy-naphthalene-7-sulfonic acid;

Carbonylbis-2-({4-[(3-amino-1-methylpyrazole-5-carbonyl) amino]-1-methylpyrrole-2-carbonyl}amino)-5-hydroxy-naphthalene-7-sulfonic acid;

Carbonylbis-2-({3-[(4-amino-1-methylpyrrole-2-carbonyl) amino]-1-methylpyrazole-5-carbonyl}amino)-5-hydroxy-naphthalene-7-sulfonic acid;

Carbonylbis-2-({4-[(3-amino-1-methylpyrazole-5- carbonyl) amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-4,6-disulfonic acid;

Carbonylbis-2-({4-[(3-amino-1-methylpyrazole-5- carbonyl) amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-5,7-disulfonic acid;

Carbonylbis-1-{[4-({4-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrrole-2-carbonyl}amino)-1-methylpyrrole-2-carbonyl]amino}naphthalene-4,6-disulfonic acid;

Carbonylbis-2-{[4-({4-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrrole-2-carbonyl}amino)-1-methylpyrrole-2-carbonyl]amino}naphthalene-4,6,8-trisulfonic acid; and

Carbonylbis-2-{[3-({4-[(4-amino-1-methylpyrrole-2-

carbonyl)amino]-1-methylpyrrole-2-carbonyl}amino)-1-methylpyrazole-5-carbonyl]amino}naphthalene-4,6,8-trisulfonic acid.

Example 8

4-4'-Carbonylbis-[2-(N-imidazolecarbonyl)-4-amino-1-methyl pyrrole] [Compound (IV), q= 1, X= imidazolyl, E= -CH=].

To a solution of 4-amino-1-methylpyrrole-2-carboxylic acid (4.00 g, 22.6 mmol as hydrochloride), sodium bicarbonate (7.56 g, 90 mmol), in water (75 ml) and 1,4-dioxane (25 ml), a solution of bis(trichloromethyl) carbonate (1.25 g, 4.2 mmol) in 1,4-dioxane (10 ml) is added dropwise, with stirring and ice-cooling. The reaction mixture is acidified to pH 1-2 with diluted hydrochloric acid, the precipitated white solid is filtered, washed with H_2O and dried to give 4-4'-carbonylbis-4-amino-1-methylpyrrole-2-carboxylic acid (3.29 g, 95% yield).

^{1}H NMR (DMSO-d_6): δ 12.1 (br, 1H, exch. with D_2O); 8.2 (s, 1H, exch. with D_2O); 7.12 (d, 1H); 6.62 (d, 1H); 3.80 (s, 3H).

To a solution of the above acid (3.29 g, 10.75 mmol) in N,N-dimethylformamide (50 ml) N,N'-carbonyldiimidazole (5.20 g, 32.6 mmol) is added portionwise, with stirring, at room temperature. After 4 hrs, the precipitated solid is filtered, washed with DMF, Et_2O and dried to give the title compound (3.90 g, 90% yield).

^{1}H NMR (DMSO-d_6): δ 8.75 (bs, 1H); 8.25 (m, 1H); 7.70 (t, 1H); 7.52 (d, 1H); 7.13 (m, 1H); 6.80 (d, 1H); 3.90 (s, 3H).

Example 9

Carbonylbis-2-({3-[(4-amino-1-methylpyrrole-2-carbonyl) amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-6,8-

disulfonic acid tetrapotassium salt [Compound (I), R= -SO_3H, p= 2, m= 2, E= -CH= and -N=].

A mixture of 2-[(3-amino-1-methylpyrazole-5-carbonyl) amino]naphthalene-6,8-disulfonic acid monopotassium salt of Example 2 (510 mg, 1.10 mmol) and 4-4'-carbonylbis-[2-(N-imidazolecarbonyl)-4-amino-1-methylpyrrole] of Example 8 (205 mg, 0.50 mmol) in N,N-dimethylformamide (20 ml) is warmed under N_2 to 50-55°C for 4 hrs. Dimethylformamide is distilled in vacuum, ethanol is added to the residue and the precipitated solid is filtered and washed. The crude is dissolved in water, passed through a sulfonic acid ion-exchange resin in H^+ form, the acid eluate of the title compound is neutralized to pH 6.5 - 7 with KOH solution and purified with reversed-phase liquid chromatography eluting with a gradient from H_2O to H_2O:MeCN 80:20. The product containing eluate is concentrated in vacuum and freeze-dried to give the yellow microcrystalline title compound (300 mg, 43% yield).

^1H NMR (DMSO-d_6): δ 10.65, 10.44 (two multiplets, 2H, exch. with D_2O); 9.01 (nm, 1H,); 8.22 (d, 1H, J=1.8 Hz); 8.2 (bs, 1H, exch. with D_2O); 8.01 (nm, 1H); 7.90 (m, 2H); 7.57 (s, 1H); 7.14, 6.93 (two doublets, 2H, J=1.8 Hz); 4.07 (s, 3H), 3.86 (s, 3H).

By proceeding analogously, with the appropriate starting materials, the following compounds can be obtained either as free or potassium salified compounds:

Carbonylbis-2-({5-[(5-amino-1-methylpyrazole-3-carbonyl) amino]-1-methylpyrazole-3-carbonyl}amino)naphthalene-6,8-disulfonic acid;

Carbonylbis-2-({4-[(5-amino-1-methylpyrazole-3-carbonyl) amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-6,8-disulfonic acid;

Carbonylbis-2-({5-[(4-amino-1-methylpyrrole-2-carbonyl)

amino]-1-methylpyrazole-3-carbonyl}amino)naphthalene-6,8-disulfonic acid;

Carbonylbis-1-({3-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-4,6,8-trisulfonic acid;

Carbonylbis-1-({3-[(4-amino-1-methylpyrrole-2-carbonyl)amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-4,6,8-trisulfonic acid;

Carbonylbis-1-({4-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-4,6,8-trisulfonic acid;

Carbonylbis-1-({3-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-4,6-disulfonic acid;

Carbonylbis-1-({4-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-4,6-disulfonic acid;

Carbonylbis-1-({3-[(4-amino-1-methylpyrrole-2-carbonyl)amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-4,6-disulfonic acid;

Carbonylbis-2-({3-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-4,6,8-trisulfonic acid;

Carbonylbis-2-({4-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-4,6,8-trisulfonic acid;

Carbonylbis-2-({3-[(4-amino-1-methylpyrrole-2-carbonyl)amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-4,6,8-trisulfonic acid;

Carbonylbis-2-({3-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-1,5-disulfonic acid;

Carbonylbis-2-({4-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-1,5-disulfonic acid;

Carbonylbis-2-({3-[(4-amino-1-methylpyrrole-2-carbonyl)amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-

1,5-disulfonic acid;

Carbonylbis-1-({3-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-8-sulfonic acid;

Carbonylbis-1-({4-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-8-sulfonic acid;

Carbonylbis-1-({3-[(4-amino-1-methylpyrrole-2-carbonyl)amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-8-sulfonic acid;

Carbonylbis-1-({3-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-4-sulfonic acid;

Carbonylbis-1-({4-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-4-sulfonic acid;

Carbonylbis-1-({3-[(4-amino-1-methylpyrrole-2-carbonyl)amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-4-sulfonic acid;

Carbonylbis-2-({3-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrazole-5-carbonyl}amino)-5-hydroxy-naphthalene-7-sulfonic acid;

Carbonylbis-2-({4-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrrole-2-carbonyl}amino)-5-hydroxy-naphthalene-7-sulfonic acid;

Carbonylbis-2-({3-[(4-amino-1-methylpyrrole-2-carbonyl)amino]-1-methylpyrazole-5-carbonyl}amino)-5-hydroxy-naphthalene-7-sulfonic acid;

Carbonylbis-2-({4-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-4,6-disulfonic acid;

Carbonylbis-2-({4-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-5,7-disulfonic acid;

Carbonylbis-1-{[4-({4-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrrole-2-carbonyl}amino)-1-methylpyrrole-2-carbonyl]amino}naphthalene-4,6-

disulfonic acid;

Carbonylbis-2-{[4-({4-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrrole-2-carbonyl}amino)-1-methylpyrrole-2-carbonyl]amino}naphthalene-4,6,8-trisulfonic acid; and

Carbonylbis-2-{[3-({4-[(4-amino-1-methylpyrrole-2-carbonyl)amino]-1-methylpyrrole-2-carbonyl}amino)-1-methylpyrazole-5-carbonyl]amino}naphthalene-4,6,8-trisulfonic acid.

Example 10

Naphthalene-1,5-diphosphonic acid tetraethyl ester.

Naphthalene-1,5-ditrifluoromethanesulfonate (16.46 g, 40 mmol) (prepared by treating 1,5-dihydroxynaphthalene with trifluoromethanesulfonic anhydride in pyridine, m.p. 112-113°C), diethyl phosphite (13.81 g, 100 mmol), dry N,N-diisopropylethylamine (15.51 g, 120 mmol), tetrakis (triphenylphosphine)palladium(0) (1.00 g, 0.86 mmol) in 50 ml N,N-dimethylformamide are heated to 95-100°C for 3 hrs. After cooling, the reaction mixture is poured into H_2O and extracted with ethyl acetate. The organic extract is washed with H_2O, diluted acid, $NaHCO_3$ solution, H_2O, dried (Na_2SO_4), concentrated under reduced pressure to 50 ml and diluted with 25 ml diethyl ether. After ice-cooling, the separated crystalline solid is filtered, washed with diethyl ether and dried to yield the title compound (12.23 g, m.p. 169-171°C, 76.4% yield).

$C_{18}H_{26}O_6P_2$ found (calc.) % : C 53.74 (54.00), H 6.53 (6.55),

EI MS : 400 $(M)^+$.

^1H NMR ($CDCl_3$): δ 8.82 (dd, 2H, J=8.7 Hz, J=1.2 Hz); 8.30 (ddd, 2H, J=1.2 Hz, J=6.9 Hz, J=15.6 Hz); 7.65 (ddd, 2H, J=3.9 Hz, J=6.9 Hz, J=8.7 Hz); 3.9-4.5 (m, 8H); 1.32 (t, 12H, J=7.2 Hz).

Example 11

3-Nitronaphthalene-1,5-diphosphonic acid tetraethyl ester. [Compound (X), R'= $-PO(OEt)_2$, p= 2].

Naphthalene-1,5-diphosphonic acid tetraethyl ester of Example 10 (10.21 g, 25.5 mmol) is dissolved portionwise in ice-cooled 96% H_2SO_4 and sulphonitric mixture (2.5 ml 90% HNO_3 in 7.5 ml 96% H_2SO_4) is added dropwise in 15 min. After 30 min in ice-cooling, the reaction mixture is poured into ice-water mixture and extracted with ethyl acetate. The organic extract is washed with H_2O, $NaHCO_3$ solution, dried, concentrated under reduced pressure to 20 ml and diluted with 30 ml cyclohexane. After ice-cooling, the separated crystalline solid is filtered, washed and dried to yield the title compound (8.48 g, m.p. 117-118.5°C, 74.7% yield).

$C_{18}H_{25}NO_8P_2$ found (calculated) % : C 48.31 (48.54), H 5.64 (5.66), N 2.98 (3.14).

^1H NMR ($CDCl_3$): δ 9.75 (dd, 1H, J=2.3 Hz, J=1.0 Hz); 8.97 (dd, 1H, J=2.3, J=16.6 Hz); 8.93 (m, 1H); 8.46 (ddd, 1H, J=1.3 Hz, J=7.1 Hz, J=15.9 Hz); 7.85 (ddd, 1H, J=3.6 Hz, J=7.1 Hz, J=8.4 Hz); 3.9-4.6 (m, 8H); 1.38 (t, 12H, J=7.2 Hz).

EI MS : 445 $(M)^+$.

Example 12

3-Aminonaphthalene-1,5-diphosphonic acid tetraethyl ester [Compound (III), R'= $-PO(OEt)_2$, p= 2].

3-Nitronaphthalene-1,5-diphosphonic acid tetraethyl ester of Example 11 (4.00 g, 9.0 mmol) dissolved in methanol (150 ml) and 1N HCl aqueous solution (10 ml) is stirred with H_2 and 5% Pd/C in a PARR apparatus until H_2 absorption ceased. After catalyst filtration on filter aid, the methanol is evaporated under reduced pressure; the residue is stirred with ethanol (10 ml) and diethyl ether (50 ml) and the separated crystalline solid is

filtered, washed and dried to yield the title compound as the hydrochloride hemihydrate (3.78 g, decomp 230-240°C, 91% yield).

$C_{18}H_{28}ClNO_6P_2.0.5H_2O$ found (calc) % : C 46.99 (46.91), H 6.32 (6.34), N 3.02 (3.04).

^1H NMR ($CDCl_3$) : δ 8.3 (bs, 1H); 9.03 (d, 1H, J=2.1 Hz); 8.77 (d, 1H, J=8.5 Hz); 8.50 (dd, 1H, J=2.1 Hz, J=16.6 Hz); 8.26 (ddd, 1H, J=1.3 Hz, J=7.2 Hz, J=15.6 Hz); 7.65 (ddd, 1H, J=3.9 Hz, J=7.2 Hz, J=8.5 Hz); 3.9-4.5 (m, 8H); 1.3-1.5 (m, 12H).

Example 13

2-[(4-Nitro-1-methylpyrrole-2-carbonyl)amino]naphthalene-4,8-diphosphonic acid tetraethyl ester [Compound (VIII), R'= $-PO(OEt)_2$, p= 2, Z= NO_2, E= -CH=].

To an ice-cooled solution of 3-aminonaphthalene-1,5-diphosphonic acid tetraethyl ester of Example 12 (3.75 g, 8.14 mmol, as hydrochloride hemihydrate) and triethylamine (3.75 ml, 27 mmol) in dichlorometane (60 ml, ethanol free) 4-nitro-1-methylpyrrole-2-carboxylic acid chloride (1.89 g, 10 mmol) dissolved in dichloromethane (15 ml) is added dropwise. After leaving 4 hrs at room temperature, the organic phase is washed with H_2O, 1N HCl followed by 5% $NaHCO_3$ solution, dried (Na_2SO_4) and evaporated under reduced pressure to small volume and then purified by flash-chromatography on Silica Gel 60 (CH_2Cl_2 95-MeOH 5). The solid residue is taken up with diethyl ether, filtered and dried, to afford the title compound (4.17 g, m.p. 250.5-252.5°C, 90% yield).

$C_{24}H_{31}N_3O_9P_2$ found (calc.): C 50.87 (50.79), H 5.53 (5.51), N 7.35 (7.40).

^1H NMR ($CDCl_3$): δ 9.77 (s, 1H); 9.23 (d, 1H, J=2.2); 8.65 (dd, 1H, J=1.4 Hz, J=8.4 Hz); 8.55 (dd, 1H, J=2.2 Hz, J= 17.4 Hz); 8.13 (ddd, 1H, J=1.4 Hz, J=7.3 Hz, J=16.0 Hz); 7.3-7.7 (m, 3H); 3.9-4.5 (m, 8H); 3.87 (s, 3H); 1.1-1.6 (m, 12H).

EI MS : 567 $(M)^+$.

Example 14

2-[(4-Amino-1-methylpyrrole-2-carbonyl)amino]naphthalene-4,8-diphosphonic acid tetraethyl ester, hydrochloride [Compound (II), R'= $-PO(OEt)_2$, p= 2, m= 1, E= -CH=].

2-[(4-Nitro-1-methylpyrrole-2-carbonyl)amino]naphthalene-4, 8-diphosphonic acid tetraethyl ester of Example 13 (4.45 g, 7.31 mmol) dissolved in methanol (150 ml) and 1N HCl (7.5 ml) is hydrogenated in presence of 5% Pd/C in a PARR apparatus until H_2 absorption ceased. After catalyst filtration on filter aid, the methanol is evaporated under reduced pressure and the residue is dried in vacuum and passed to the acylation step without further purification.

^1H NMR ($CDCl_3$): δ 9.6 (s, 1H); 9.05 (m, 1H); 8.67 (dd, 1H, J=1.9 Hz, J=17.6 Hz); 8.67 (d, 1H, J=8.6 Hz); 8.12 (dd, 1H, J=6.5 Hz, J=15.9 Hz); 7.75 (s, 1H); 7.55 (m, 1H); 6.87 (s, 1H); 3.9-4.4 (m, 8H); 3.75 (s, 3H); 1.0-1.4 (m, 12H).

Example 15

2-({4-[(4-Nitro-1-methylpyrrole-2-carbonyl)amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-4,8-diphosphonic acid tetraethyl ester [Compound (V), R'= -$PO(OEt)_2$, p= 2, m= 2, Z= -NO_2, E= -CH=].

2-[(4-Amino-1-methylpyrrole-2-carbonyl)amino]naphthalene-4, 8-diphosphonic acid tetraethyl ester of Example 14 (7.3 mmol as hydrochloride) and triethylamine (3.5 ml, 25 mmol) in dichloromethane (100 ml, ethanol free) are treated dropwise, with ice-bath cooling, with 4-nitro-1-methylpyrrole-2-carboxylic acid chloride (1.41 g, 7.5 mmol) dissolved in dichloromethane (15 ml). After leaving 1 h in ice and 1 h at room temperature, the organic phase is washed with acid and $NaHCO_3$ solutions,

dried (Na_2SO_4) and evaporated under reduced pressure. The crude residue redissolved in ethanol (20 ml) is scratched to induce crystal formation; crystallization is completed with diethyl ether (20 ml) and the separated crystalline yellow solid is filtered, washed with an ethanol-diethyl ether 1:1 mixture and dried at 50°C under reduced pressure to yield the title compound (4.50 g, m.p. 163-168°C, 89 % yield).

$C_{30}H_{37}N_5O_{10}P_2$ found (calc.) % : N 9.85 (10.16).

(-)FAB MS : 688 $(M-H)^-$.

^1H NMR (DMSO-d_6): δ 10.34, 10.49 (two singlets, 2H); 9.23 (s, 1H); 8.61 (d, 1H, J=8.4 Hz); 8.57 (dd, 1H, J=2.0 Hz, J=17.6 Hz); 8.12 (dd, 1H, J=7.0 Hz, J=16.1 Hz); 7.63 (ddd, 1H, J=4.2 Hz, J=7.0 Hz, J=8.4 Hz); 7.60, 8.19 (two doublets, 2H, J=1.8 Hz); 7.26, 7.37 (two doublets, J=1.8 Hz); 4.0-4.2 (m, 8H); 3.90, 3.96 (two singlets, 6H); 1.1-1.3 (m, 12H).

Example 16

2-({4-[(4-Amino-1-methylpyrrole-2-carbonyl)amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-4,8-diphosphonic acid tetraethyl ester hydrochloride [Compound (II), R'= $-PO(OEt)_2$, p = 2, m = 2, E = -CH=].

2-({4-[(4-Nitro-1-methylpyrrole-2-carbonyl)amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-4,8-diphosphonic acid tetraethyl ester of Example 15 (4.50 g, 6.52 mmol) dissolved in methanol (350 ml) and aqueous 1N HCl (7.0 ml) is hydrogenated with 5% Pd/C (500 mg) in a PARR apparatus until H_2 absorption ceased. After catalyst filtration, methanol is evaporated under reduced pressure. The residue is taken up in diethyl ether and the separated microcrystalline solid is filtered, washed and dried at 60°C under reduced pressure to give the title compound (4.43 g, 96% yield) as hydrochloride.

$C_{30}H_{40}ClN_5O_8P_2$ found (calc.) % : C 49.93 (51.76), H 5.93 (5.79), Cl 5.00 (5.09), N 9.61 (10.06).

(-)FAB MS : 658 $(M-H)^-$.

^1H NMR (DMSO-d_6): δ 10.13, 10.46 (two singlets, 2H); 9.85 (bs, 3H); 9.23 (s, 1H); 8.60 (d, 1H, J=8.5 Hz); 8.56 (dd, 1H, J=2.0 Hz, J=17.3 Hz); 8.12 (dd, 1H, J=7.3 Hz, J=17.0 Hz); 7.64 (ddd, 1H, J=3.5 Hz, J=7.3 Hz, J=8.5 Hz); 7.26, 7.36 (two doublets, 2H, J=1.8 Hz); 7.00, 7.10 (two doublets, 2H, J=2.0 Hz); 4.0-4.2 (m, 8H); 3.89 (s, 6H); 1.2-1.3 (m, 12H).

Example 17

Carbonylbis-2-{[4-({4[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrrole-2-carbonyl}amino)-1-methylpyrrole-2-carbonyl]amino}naphthalene-4,8-diphosphonic acid octaethyl ester [Compound (I), R' = $-PO(OEt)_2$, p = 2 , m = 3, E = -N= and -CH=].

A mixture of 2-({4-[(4-amino-1-methylpyrrole-2-carbonyl)amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-4,8-diphosphonic acid tetraethyl ester hydrochloride of Example 16 (300 mg, 0.43 mmol) and 3-3'-carbonylbis-[5-(N-imidazolecarbonyl)-3-amino-1-methylpyrazole] of Example 6 (82 mg, 0.20 mmol) in N,N-dimethylformamide (10 ml) is warmed under N_2 at 40-50°C for 2 hrs. Dimethylformamide is distilled in vacuum; the residue, redissolved in dichloromethane, is washed with H_2O, 0.5N HCl, $NaHCO_3$ solution, dried and evaporated under reduced pressure. The crude residue is purified by flash-chromatography on Silica-Gel 60 (CH_2Cl_2 85 - EtOH 15).The solid residue is taken up with ethyl acetate, filtered and dried to afford the title compound (160 mg, 50% yield) as a crystalline pale-brown solid.

^1H NMR (DMSO-d_6) : δ 10.52, 10.48, 10.09 (three singlets, 3H, exch. with D_2O); 9.4 (bs, 1H, exch. with D_2O); 9.25 (s, 1H); 8.7-8.5 (m, 2H); 8.13 (dd, 1H, J=7.0 Hz, J=15.8 Hz); 7.64 (ddd, 1H, J=3.7 Hz, J=7.0 Hz, J=7.6 Hz); 7.4-7.1 (m, 4H); 7.11 (s, 1H); 4.3-3.9 (m, 8H); 4.01 (s, 3H); 3.90, 3.89 (two singlets, 6H);

1.4-1.1 (m, 12 H).

(+)FAB MS : 1591 $(M+H)^+$, 1177, 783, 538.

(-)FAB MS : 1589 $(M-H)^-$.

By proceeding analogously the alkyl and aryl-alkyl esters of the following compounds can be obtained:

Carbonylbis-2-({3-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-4,8-diphosphonic acid;

Carbonylbis-2-({4-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-4,8-diphosphonic acid;

Carbonylbis-2-({3-[(4-amino-1-methylpyrrole-2-carbonyl)amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-4,8-diphosphonic acid;

Carbonylbis-1-({3-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-4,6-diphosphonic acid;

Carbonylbis-1-({4-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-4,6-diphosphonic acid;

Carbonylbis-1-({3-[(4-amino-1-methylpyrrole-2-carbonyl)amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-4,6-diphosphonic acid;

Carbonylbis-1-({3-[(4-amino-1-methylpyrrole-2-carbonyl)amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-6,8-diphosphonic acid;

Carbonylbis-1-({3-[(4-amino-1-methylpyrrole-2-carbonyl)amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-5,7-diphosphonic acid;

Carbonylbis-1-{[4-({4-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrrole-2-carbonyl}amino)-1-methylpyrrole-2-carbonyl]amino}naphthalene-4,6-diphosphonic acid;

Carbonylbis-2-{[4-({4-[(5-amino-1-methylpyrazole-3-carbonyl)amino]-1-methylpyrrole-2-carbonyl}amino)-1-

methylpyrrole-2-carbonyl]amino}naphthalene-4,8-diphosphonic acid;

Carbonylbis-1-({4-[(3-amino-1-methylpyrazole-5- carbonyl) amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-6,8-diphosphonic acid; and

Carbonylbis-1-({4-[(3-amino-1-methylpyrazole-5- carbonyl) amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-5,7-diphosphonic acid.

Example 18

Carbonylbis-2-{[4-({4-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrrole-2-carbonyl}amino)-1-methylpyrrole-2-carbonyl]amino}naphthalene-4,8-diphosphonic acid and tetrasodium salt [Compound (I), R' = $-PO(OH)_2$, p= 2, m = 3, E = -N= and -CH=].

To an ice-cooled solution of the octaethyl ester compound obtained in Example 17 (135 mg, 0.085 mmol) in dry dichloromethane (20 ml), bromotrimethylsilane (0.8 ml) is added dropwise with stirring . After leaving 48 hrs at room-temperature, the organic volatiles are evaporated under reduced pressure. The residue is taken up with acetone (10 ml) and H_2O (100 mg) is added. After stirring for 4 hrs, the separated microcrystalline yellow solid is filtered, washed with acetone and vacuum dried to give the title acid (115 mg, near quantitative yield).

^1H NMR (DMSO-d_6): δ 10.52, 10.35, 10.06 (three singlets, 3H, exch. with D_2O); 9.3 (bs, 1H, exch. with D_2O); 9.10 (s, 1H); 8.68 (d, 1H, J=8.7 Hz); 8.48 (dd, 1H, J=2.1 Hz, J=17.1 Hz); 8.05 (ddd, 1H, J=1.1 Hz, J=6.2 Hz, J=15.1 Hz); 7.53 (m, 1H); 7.4-7.1 (m, 4H); 7.10 (s, 1H); 4.02 (s, 3H); 3.89 (s, 6H).

The acid thus obtained (115 mg, 0.084 mmol) is suspended in H_2O (10 ml) and neutralized with 0.1N NaOH to pH 5.5-6.0. The solution thus obtained is filtered, concentrated under reduced pressure to small volume and freeze-dried

to microcrystalline pale-yellow title tetrasodium salt (145 mg, air equilibrated).

By analogous procedures, the following compounds can be obtained either as free or sodium salified acids:

Carbonylbis-2-({3-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrazole-5-carbonyl}amino) naphthalene-4,8-diphosphonic acid;

Carbonylbis-2-({4-[(3-amino-1-methylpyrazole-5-carbonyl) amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-4,8-diphosphonic acid;

Carbonylbis-2-({3-[(4-amino-1-methylpyrrole-2-carbonyl) amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-4,8-diphosphonic acid;

Carbonylbis-1-({3-[(3-amino-1-methylpyrazole-5-carbonyl) amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-4,6-diphosphonic acid;

Carbonylbis-1-({4-[(3-amino-1-methylpyrazole-5-carbonyl) amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-4,6-diphosphonic acid;

Carbonylbis-1-({3-[(4-amino-1-methylpyrrole-2-carbonyl) amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-4,6-diphosphonic acid;

Carbonylbis-1-({3-[(4-amino-1-methylpyrrole-2-carbonyl) amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-6,8-diphosphonic acid;

Carbonylbis-1-({3-[(4-amino-1-methylpyrrole-2-carbonyl) amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-5,7-diphosphonic acid;

Carbonylbis-1-{[4-({4-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrrole-2-carbonyl}amino)-1-methylpyrrole-2-carbonyl]amino}naphthalene-4,6-diphosphonic acid;

Carbonylbis-2-{[4-({4-[(5-amino-1-methylpyrazole-3-carbonyl)amino]-1-methylpyrrole-2-carbonyl}amino)-1-methylpyrrole-2-carbonyl]amino}naphthalene-4,8-

diphosphonic acid;

Carbonylbis-1-({4-[(3-amino-1-methylpyrazole-5-carbonyl) amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-6,8-diphosphonic acid; and

Carbonylbis-1-({4-[(3-amino-1-methylpyrazole-5-carbonyl) amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-5,7-diphosphonic acid.

Example 19

Intramuscular injection 40 mg/ml.

An injectable pharmaceutical preparation can be manufactured by dissolving 40 g of Carbonylbis-2-({3-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methyl pyrazole-5-carbonyl}amino)naphthalene-6,8-disulfonic acid tetrapotassium salt in water for injection (1000 ml) and sealing ampoules of 1-10 ml.

Example 20

Capsules, each dosed at 0.200 g and containing 20 mg of the active substance can be prepared.

Composition for 500 capsules:

Carbonylbis-2-({3-[(3-amino-1-methylpyrazole-5-carbonyl) amino]-1-methyl pyrazole-5-carbonyl}amino)naphthalene-6,8-disulfonic acid tetrapotassium salt	10 g
Lactose	80 g
Corn starch	5 g
Magnesium stearate	5 g

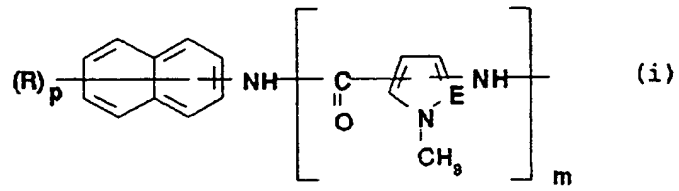
This formulation is encapsulated in two-piece hard gelatin capsules and dosed at 0.200 g for each capsule.

CLAIMS

1. A compound of formula (I)

B-CO-B (I)

wherein each of the B groups, which are the same, is a group (i)



(i)

wherein
m is an integer of 1 to 6;
p is an integer of 1 to 3;
E is a group -CH= or -N=;
each of the R groups, which are the same, is a free or esterified acid group; and the pharmaceutically acceptable salts thereof;
and wherein when m is 1, then E is -N=; whereas when m is an integer of 2 to 6, then at least one of the E groups is -N=.

2. A compound of formula (I) as defined in claim 1, wherein each of the B groups, which are the same, is a group (i), as defined in claim 1, wherein
m is 2 or 3;
one of the E groups is -N=, the others being -N= or —CH=; p is 2 or 3; and each of the R groups, which are the same, is a free or esterified phosphonic or sulfonic acid group; and the pharmaceutically acceptable salts thereof.

3. An ester of a compound of formula (I) as defined in claims 1 or 2, wherein said ester is a C_1-C_6 alkyl

ester or a phenyl-C_1-C_6 alkyl ester.

4. A compound selected from the group consisting of:

Carbonylbis-2-({3-[(3-amino-1-methylpyrazole-5-carbonyl) amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-6,8-disulfonic acid;

Carbonylbis-2-({4-[(3-amino-1-methylpyrazole-5-carbonyl) amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-6,8-disulfonic acid;

Carbonylbis-2-({3-[(4-amino-1-methylpyrrole-2-carbonyl) amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-6,8-disulfonic acid;

Carbonylbis-2-({5-[(5-amino-1-methylpyrazole-3-carbonyl) amino]-1-methylpyrazole-3-carbonyl}amino)naphthalene-6,8-disulfonic acid;

Carbonylbis-2-({4-[(5-amino-1-methylpyrazole-3-carbonyl) amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-6,8-disulfonic acid;

Carbonylbis-2-({5-[(4-amino-1-methylpyrrole-2-carbonyl) amino]-1-methylpyrazole-3-carbonyl}amino)naphthalene-6,8-disulfonic acid;

Carbonylbis-1-({3-[(3-amino-1-methylpyrazole-5-carbonyl) amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-4,6,8-trisulfonic acid;

Carbonylbis-1-({4-[(3-amino-1-methylpyrazole-5-carbonyl) amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-4,6,8-trisulfonic acid;

Carbonylbis-1-({3-[(4-amino-1-methylpyrrole-2-carbonyl) amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-4,6,8-trisulfonic acid;

Carbonylbis-1-({3-[(3-amino-1-methylpyrazole-5-carbonyl) amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-4,6-disulfonic acid;

Carbonylbis-1-({4-[(3-amino-1-methylpyrazole-5-carbonyl) amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-4,6-disulfonic acid;

Carbonylbis-1-({3-[(4-amino-1-methylpyrrole-2-carbonyl) amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-4,6-disulfonic acid;

Carbonylbis-2-({3-[(3-amino-1-methylpyrazole-5-carbonyl) amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-4,6,8-trisulfonic acid;

Carbonylbis-2-({4-[(3-amino-1-methylpyrazole-5-carbonyl) amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-4,6,8-trisulfonic acid;

Carbonylbis-2-({3-[(4-amino-1-methylpyrrole-2-carbonyl) amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-4,6,8-trisulfonic acid;

Carbonylbis-2-({3-[(3-amino-1-methylpyrazole-5-carbonyl) amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-1,5-disulfonic acid;

Carbonylbis-2-({4-[(3-amino-1-methylpyrazole-5-carbonyl) amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-1,5-disulfonic acid;

Carbonylbis-2-({3-[(4-amino-1-methylpyrrole-2-carbonyl) amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-1,5-disulfonic acid;

Carbonylbis-1-({3-[(3-amino-1-methylpyrazole-5-carbonyl) amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-8-sulfonic acid;

Carbonylbis-1-({4-[(3-amino-1-methylpyrazole-5-carbonyl) amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-8-sulfonic acid;

Carbonylbis-1-({3-[(4-amino-1-methylpyrrole-2-carbonyl) amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-8-sulfonic acid;

Carbonylbis-1-({3-[(3-amino-1-methylpyrazole-5-carbonyl) amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-4-sulfonic acid;

Carbonylbis-1-({4-[(3-amino-1-methylpyrazole-5-carbonyl) amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-4-sulfonic acid;

Carbonylbis-1-({3-[(4-amino-1-methylpyrrole-2-carbonyl)

amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-4-sulfonic acid;

Carbonylbis-2-({3-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrazole-5-carbonyl}amino)-5-hydroxy naphthalene-7-sulfonic acid;

Carbonylbis-2-({4-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrrole-2-carbonyl}amino)-5-hydroxy naphthalene-7-sulfonic acid;

Carbonylbis-2-({3-[(4-amino-1-methylpyrrole-2-carbonyl)amino]-1-methylpyrazole-5-carbonyl}amino)-5-hydroxy naphthalene-7-sulfonic acid;

Carbonylbis-2-({4-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-4,6-disulfonic acid;

Carbonylbis-2-({4-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-5,7-disulfonic acid;

Carbonylbis-1-{[4-({4-[(3-amino-1-methylpyrazole-5-carbonyl)-amino]-1-methylpyrrole-2-carbonyl}amino)-1-methyl-pyrrole-2-carbonyl]amino}naphthalene-4,6-disulfonic acid;

Carbonylbis-2-{[4-({4-[(3-amino-1-methylpyrazole-5-carbonyl)-amino]-1-methylpyrrole-2-carbonyl}amino)-1-methyl-pyrrole-2-carbonyl]amino}naphthalene-4,6,8-trisulfonic acid;

Carbonylbis-2-{[3-({4-[(4-amino-1-methylpyrrole-2-carbonyl)-amino]-1-methylpyrrole-2-carbonyl}amino)-1-methyl-pyrazole-5-carbonyl]amino}naphthalene-4,6,8-trisulfonic acid;

Carbonylbis-2-({3-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-4,8-diphosphonic acid;

Carbonylbis-2-({4-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-4,8-diphosphonic acid;

Carbonylbis-2-({3-[(4-amino-1-methylpyrrole-2-carbonyl)amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-

4,8-diphosphonic acid;

Carbonylbis-1-({3-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-4,6-diphosphonic acid;

Carbonylbis-1-({4-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-4,6-diphosphonic acid;

Carbonylbis-1-({3-[(4-amino-1-methylpyrrole-2-carbonyl)amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-4,6-diphosphonic acid;

Carbonylbis-1-({3-[(4-amino-1-methylpyrrole-2-carbonyl)amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-6,8-diphosphonic acid;

Carbonylbis-1-({3-[(4-amino-1-methylpyrrole-2-carbonyl)amino]-1-methylpyrazole-5-carbonyl}amino)naphthalene-5,7-diphosphonic acid;

Carbonylbis-2-{[4-({4-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrrole-2-carbonyl}amino)-1-methylpyrrole-2-carbonyl]amino}naphthalene-4,8-diphosphonic acid;

Carbonylbis-1-{[4-({4-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrrole-2-carbonyl}amino)-1-methylpyrrole-2-carbonyl]amino}naphthalene-4,6-diphosphonic acid;

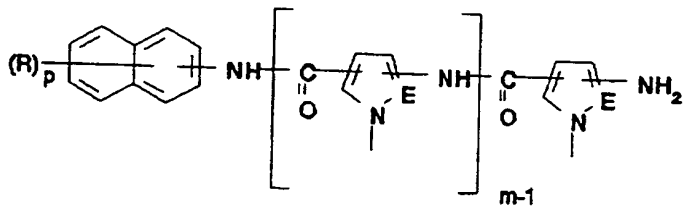
Carbonylbis-2-{[4-({4-[(5-amino-1-methylpyrazole-3-carbonyl)amino]-1-methylpyrrole-2-carbonyl}amino)-1-methylpyrrole-2-carbonyl]amino}naphthalene-4,8-diphosphonic acid;

Carbonylbis-1-({4-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-6,8-diphosphonic acid;

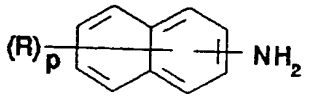
Carbonylbis-1-({4-[(3-amino-1-methylpyrazole-5-carbonyl)amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-5,7-diphosphonic acid;

and the C_1-C_6-alkyl and phenyl-C_1-C_6-alkyl esters and the pharmaceutically acceptable salts thereof.

5. A process for the preparation of a compound of formula (I), as defined in claim 1, or a salt thereof, the process comprising reacting a compound of formula (II) or (III), respectively



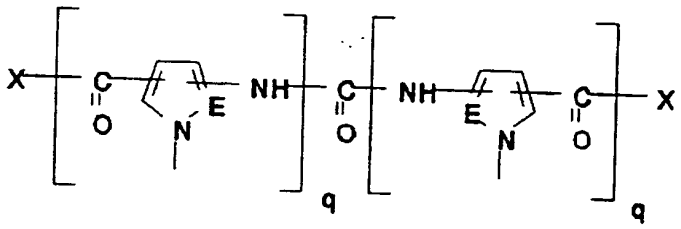
(II)



(III)

wherein

m, p, E and R are as defined in claim 1, or a salt thereof, with a compound of formula (IV)



(IV)

wherein

each of the X groups, which may be the same or different, is a good leaving group, E is as defined in claim 1, q is 0 to 6 and wherein, when a compound of formula (IV) is reacted with a compound of formula (II), then q is 0 to 5 in such a way that [q+(m-1)] is 0 to 5, whereas when a compound of formula (IV) is reacted with a compound of formula (III), then q is an integer of 1 to 6 and, if desired, converting a compound of formula (I) into another compound of formula (I), and/or, if desired, salifying a compound of formula (I) thus obtained, and/or, if desired,

obtaining a free acid of formula (I) from an ester or a salt thereof, and/or, if desired, esterifying an acid of formula (I).

6. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and/or diluent and, as an active principle, a compound of formula (I), as defined in claim 1, or a pharmaceutically acceptable salt thereof.

7. A compound of formula (I), as defined in claim 1, or a pharmaceutically acceptable salt thereof, for use as a medicament.

8. A compound of formula (I), as defined in claim 1, or a pharmaceutically acceptable salt thereof, for use as anti-lentivirus agent.

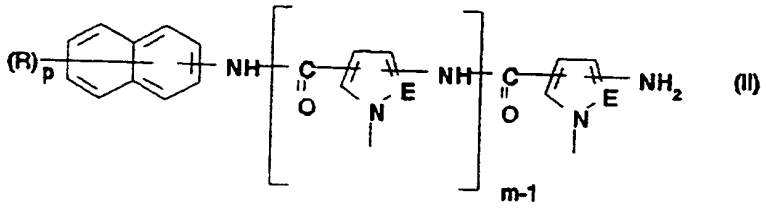
9. A compound of formula (I), as defined in claim 1, for use as an angiogenesis inhibitor.

10. A compound of formula (I), as defined in claim 1, for prophylactic and/or therapeutic use in a disease state in which TNFα plays a detrimental role.

11. A compound of formula (I), as defined in claim 1, or a pharmaceutically acceptable salt thereof, for use in ameliorating the symptoms manifested by a human patient who is seropositive diseased, stressed or pathological as a result of infection with a lentivirus or who is suffering from lentivirus-induced disease.

12. Products containing a compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined in claim 1, and a second active agent as a combined preparation for simultaneous, separate or sequential use in the treatment of a human patient suffering from lentivirus infection.

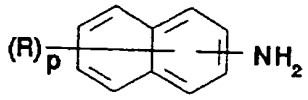
13. A compound of formula (II) or a salt thereof



(II)

wherein m, p, E and R are as defined in claim 1.

14. A compound of formula (III)



(III)

wherein p is as defined in claim 1 and R is a free, salified or esterified phosphonic acid group.

The Patent Office

S2

Application No:	GB 9603213.1	**Examiner:**	Peter Davey
Claims searched:	1-12	**Date of search:**	4 April 1997

Patents Act 1977
Search Report under Section 17

Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

UK Cl (Ed.O): C2C (CKD, CRB); C2P

Int Cl (Ed.6): C07D, C07F

Other: Online: CAS ONLINE

Documents considered to be relevant:

Category	Identity of document and relevant passage		Relevant to claims
X	GB 2260134 A	(FARMITALIA CARLO ERBA), see eg. claims 1, 5 and 6	1, 6, 7 and 9 at least
X	WO 95/23806 A2	(PHARMACIA), see eg. claims 1 and 7-9	1 and 6-12 at least
X	WO 94/23718 A1	(PHARMACIA/FARMITALIA CARLO ERBA), see eg. claims 1, 6 and 7	1, 6-8 and 11-12 at least
X	WO 91/10649 A1	(FARMITALIA CARLO ERBA), see eg. claims 1 and 7-10	1, 6-7 and 9-10 at least

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.